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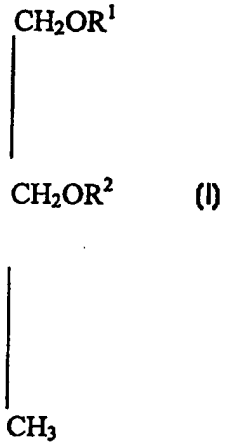
(54) Title: PRESENTATION OF BIOACTIVES

(57) Abstract

Compounds of 1,2–propane diol linked structure (I), when for use in therapy, wherein R^1 or R^2 comprises an acyl or fatty alcohol group derived from a C_{12-30} preferably C_{16-30} fatty acid desirably with two or more cis or trans double bonds, or any other nutrient, drug or other bioactive residue, such that at least one of R^1 or R^2 comprises an acyl or fatty alcohol group as defined above, and wherein where both R^1 or R^2 comprises acyl or fatty alcohol groups they may be the same or different.



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PRESENTATION OF BIOACTIVES

Field

The specification relates to the presentation of bioactives, in which term we include a drug, essential nutrient or any other compound to be administered to the human or animal body in therapy or maintenance of health.

In particular, the specification relates to the presentation of such bioactives in a form in which they are lipophilic so that they can pass lipid barriers in the body readily, or to the presentation of two bioactives in the same molecule (where at least one of the bioactives is a fatty acid or fatty alcohol), or to the presentation of bioactives in a form which serves both aims. From a drug regulatory viewpoint it is a great advantage to have two bioactives presented as a single molecule rather than as two separate entities. There may also be advantages in presenting known bioactives in novel ways. Those advantages include increased lipophilicity, the additive effects of two bioactives which are not normally presented together, and the sometimes synergistic effects of such bioactives .

Specifically, the invention concerns the linking of bioactives through a 1,2-propane diol link molecule and the usefulness of these compounds in therapy and/or the maintenance of health.

Published Material

Concepts such as are discussed above have received no great attention in the published patent and general literature but there is material on certain specific natural diol derivatives and on nutritional and pharmaceutical uses of certain specific diol esters. A source paper in the general literature is Bergelson et al (Biochim., Biophys. Acta 116 (1996) 511-520 describing inter alia long chain diesters of 1,3-propane diol. Little is said of the acid moieties but dioleates are identified. In the patent literature edible fat mimetics are for example proposed by Nabisco in EPA-0 405 873 and EPA-0 405 874 and include linolenic acid esters (this term indicating the "alpha" isomer when not qualified otherwise) and arachidonic acid

esters of, apparently, 1,4-butane diol. Unilever's U.K. specification 2 161 477 (equivalent to EPA-0 161 114) concerns the growth and economic yield of plants, using inter alia 1,3-propane diol esters of linoleic acid

and linolenic acid (again no doubt the alpha isomer). Anti-ulcer drugs of 2,3 butanediol esters are described in SS Pharmaceutical Co.'s EPA-0 056 189. Sundry pharmaceutical actions of propane-1,3-diol esters of short chain fatty acids are disclosed in Sanofi EPA-0 018 342. More distantly perhaps, Terumo K.K. in EPA-0 222 155 link 5-fluoro uracil to alpha linolenic acid, dihomo gamma linolenic acid, or eicosapentaenoic acid through a group -CH(R)-0- where R = methyl etc. as, inter alia, anti-cancer agents.

Lipid Barriers

Many drugs act at the cell membrane surface by combining with cell surface receptors, or alternatively are taken into cells by specific transport systems. However, there are many drugs which, while they act within cells by modifying one of many different functions such as nucleic acid functions, the actions of intracellular enzymes, or the behaviour of systems like the lysosomes or the microtubules, are not able to penetrate cells effectively. There may be no receptors and transport systems with which they can link, or these systems may transport the drug into the cell at a less then optimum rate. Equally drugs may penetrate intracellular membranes such as mitochondrial and nuclear membranes at less than optimum rates.

There are other barriers to drug movements which are recognised as important. One of particular significance is the blood-brain barrier, which has many of the characteristics of the cell membrane. There are many drugs which have difficulty in reaching adequate concentrations in the brain because of this barrier. Another is the skin: until a few years ago drugs were applied to the skin only if their purpose was to act on the skin. However, it has been recognised that the skin can be an appropriate route for getting drugs with systemic

actions into the body, and as a result more and more compounds are being administered by variations of patch technology.

All three types of barriers, the cell membrane and intracellular membranes, the blood-brain barrier and the skin have an important feature in common, they are substantially composed of lipids. What this means is that they are impermeable to primarily water-soluble drugs unless these drugs can be carried across the membrane by a receptor or transport system.

In contrast, lipophilic substances are able to cross the barriers more readily without the need for any specific receptor or transport system.

Classes of Bioactives Requiring Passage Through Lipid Barriers

Drugs whose pharmacokinetic behaviour may be improved by increased lipophilicity, listed by route of entry, are as follows:

Cell entry: drugs particularly likely to benefit are those that act primarily intracellularly. These include:

a. All anti-inflammatory drugs, whether steroid or non-steroid;

b. All cytotoxic drugs used in the management of cancer;

c. All antiviral drugs; .

d. All other drugs that have to enter cells in order to achieve optimum effects, in particular drugs which act on DNA or RNA, or on enzymes located intracellularly, or on second messenger systems, or on microtubules, mitochondria, lysosomes, or any other intracellular organelle.

e. Steroid hormones and other hormones that act intracellularly, such as oestrogens, progestins, androgenic hormones and dehydroepiandrosterone.

2. Blood-brain barrier: all drugs acting on the central nervous systems will have their transport improved by this technique. This includes all drugs used in psychiatry, all drugs used in cerebral infections with any organism or in cerebral cancer and all other drugs acting on nerve cells such as anti-epileptic drugs and others acting on neurological disorders such as multiple sclerosis, amyotrophic lateral sclerosis, Huntington's chorea and others.

3. Skin: as with the blood-brain barrier, all drugs that may be required to penetrate the skin to achieve a systemic effect will benefit from their conversion to a fatty acid derivatives.

For example, the approach discussed is applicable to amino acids. Of particular interest are those which seem to play roles in the regulation of cell function as well as acting as components of proteins. Examples include tryptophan (a precursor of 5-hydroxytryptamine [5-HT], a key regular of nerve and muscle function), phenylalanine (a precursor of catecholamines) and arginine (a regulator of the synthesis of nitric oxide which also plays important roles in controlling cellular activities).

Properties Conferred Generally

Generally the compounds proposed herein have many advantages in addition to their lipophilicity. For example, two moieties of a given fatty acid may be delivered, in a form which is readily incorporated into the body as an oral, parenteral or topical formulation; which is very well tolerated with none of the side effects associated, for example, with free fatty acids; which is not too stable to be properly utilised; and which is

much more readily synthesised than the corresponding triglyceride with three moieties of the same fatty acid attached.

When two different fatty acids are to be delivered, the advantages are as before plus the ability to administer simultaneously two materials with different biological actions in a single molecule. This avoids the regulatory problems which ensue when two materials are administered as separate compounds. When two drugs are delivered as separate molecules, regulatory authorities normally require each drug to be studied alone as well as in combination. If the two are combined in a single molecule, only the single molecule needs to be studied, greatly reducing the cost of development.

Where actives other than fatty acids are present there are similar advantages. The compounds allow drugs or other compounds to be administered in the form of relatively l

lipophilic compounds which release the active moieties relatively easily, and which are well tolerated on oral, topical or parenteral administration. Their lipophilicity enables them to be absorbed partially through the lymphatic system, so by-passing the liver; to cause less gastrointestinal irritation than with many compounds; and to facilitate transport of drugs and other agents across lipophilic barriers such as the skin, the cell membrane and the bloodbrain barrier.

There is evidence that interesting specific properties in addition to ready passage of lipid barriers can be conferred on many drugs by making them more lipophilic. These properties include prolonged duration of action, reduction of side effects especially gastrointestinal, bypassing of first-pass liver metabolism and, potentially, site specific delivery of different materials.

Fatty Acid Derivatives; Effects of the Fatty Acids

The transport of actives across lipid membranes may be improved by linking them via an intermediate link to, in particular, gamma-linolenic acid (GLA) or dihomogammalinolenic acid (DGLA), two fatty acids which in themselves have a range of desirable effects. Linkage also enables bioactive substances to be co-delivered in the same molecule with fatty acids which in themselves have desirable actions, irrespective of any transport advantages. Other fatty acids, such as any of the essential fatty acids (EFAS) and in particular the twelve natural acids of the n-6 and n-3 series EFAs (fig. 1), can be used. Of these twelve, arachidonic acid, adrenic acid, stearidonic acid, eicosapentaenoic acid and docosahexaenoic acid are of particular interest because they in themselves have particularly desirable effects. Furthermore, any fatty acid, suitably C12-C30 or C16-C30 and desirably with two or more cis or trans carbon-carbon double bonds may also be of use. Use may be in the form of the fatty acid or the corresponding fatty alcohol. Conjugated linoleic and columbinic acids are examples of fatty acids which in themselves have valuable properties and are likely to be of particular use. References to fatty acids are accordingly to be read herein as to both forms, except where the chemistry of one or
the other specifically is under discussion. The desirable properties of GLA and DGLA however, make them especially valuable for the purpose.

The essential fatty acids as set out in Figure 1, which in nature are of the all -cis configuration, are systematically named as derivatives of the corresponding octadecanoic, eicosanoic or docosanoic acids, e.g. z,z-octadeca -9, 12- dienoic acid or z,z,z,z,z,z -docosa- 4, 7, 10, 13, 16, 19 hexaenoic acid, but numerical designations based on the number of carbon atoms, the number of centres of unsaturation and the number of carbon atoms from the end of the chain to where the unsaturation begins, such as, correspondingly, 18:2n-6 or 22:6n-3 are convenient. Initials, e.g., EPA and shortened forms of the name e.g. eicosapentaenoic acid are used as trivial names in some of the cases.

FIGURE 1

n-6 EFAs		n-3 EFAs
18:2n-6 Linoleic acid (LA)		18:3n-3 α-linolenic acid (ALA)
↓	δ-6-desaturase	↓
18:3n-6 γ-Linolenic acid (GLA)		18:4n-3 Stearidonic acid, (SA)
↓	elongation	↓
20:3n-6 Dihomo-γ-linolenic acid (DGLA)		20:4n-3 Eicosatetraenoic acid
↓	δ-5-desaturase	↓
20:4n-6 Arachidonic acid (AA)		20: 5n-3 Eicosapentaenoic acid (EPA)
↓	elongation	↓
22:4n-6 Adrenic acid (AdrA)		22:5n-3
↓	δ-4-desaturase	↓
22:5n-6		22-6n-3 Docosahexaenoic acid (DHA)

GLA and DGLA

In their own right GLA and DGLA have been shown to have anti-inflammatory effects, to lower blood pressure, to inhibit platelet aggregation, to lower cholesterol levels, to inhibit cancer cell growth, to reduce dyskinetic movements, to relieve breast pain, to improve calcium absorption and enhance its deposition in bone, to reduce the adverse effects of ionising radiation, to treat various psychiatric disorders, to cause vasodilation, to improve renal function,

to treat the complications of diabetes, to dilate blood vessels and so on. Actives linked to GLA and DGLA will therefore not only become more lipophilic, enhancing penetration across all membranes, the skin and the blood brain barrier, but are also likely to exhibit new and additional therapeutic effects.

Other fatty acids likely to be of especial value in this context are arachidonic acid and docosahexaenoic acid which are major constituents of all cell membranes; adrenic acid; and stearidonic acid and eicosapentaenoic acid which have ranges of desirable properties similar to those of GLA and DGLA. Fatty acids not included in the fatty acids of Figure 1 which are of particular interest are conjugated linoleic acid (cLA) and columbinic acid (CA). cLA has a range of interesting effects in treating and preventing cancer, in promoting growth particularly of protein-containing tissues, in preventing and treating cardiovascular disease and as an antioxidant. CA has many of the properties of essential fatty acids.

Classes of Actives Having Mutual Efficacy with Bioactive Fatty Acids

Kinds of actives to be incorporated in compounds as set out herein may be broadly stated: -

a) Drugs including antibiotics, antiprotozoals, antipsychotics, antidepressants and NSAIDs and compounds used in the treatment of cardiovascular, respiratory, dermatological, psychiatric, neurological, renal, muscular, gastrointestinal, reproductive and other diseases and in cancer.

b) Hormones

c) Amino acids

d) Vitamins particularly of the B group, and other essential nutrients.

e) Cytokines and peptides

f) Neurotransmitters and neurotransmitter precursors.

g) Phospholipid head groups such as inositol, choline, serine and ethanolamine, which may be linked directly or via the phosphate moiety.

h) Aromatic fatty acids such as phenylacetic acid, phenyl butyric acid and cinnamic acid which are of particular value in cancer treatment.

Efficacy

The combination of the therapeutic effect of a drug with the therapeutic effect of a fatty acid may be considered through examples:-

a) Psychotropic drugs may be linked to fatty acids such as GLA, DGLA, arachidonic acid, eicosapentaenoic acid or docosahexaenoic acid which have important roles in brain function, so providing a dual therapeutic effect.

b) Drugs used for the treatment of cardiovascular disease may be linked to a fatty acid which also has value in such treatment, such as eicosapentaenoic acid which lowers triglyceride levels and inhibits platelet aggregation, or GLA or DGLA which lower cholesterol levels and have vasodilator action, or arachidonic acid which is a potent cholesterol lowering agent, or DHA which has anti-arrhythmic properties.

c) Drugs used in the treatment of any form of inflammation may be linked to a fatty acid such as gammalinolenic acid, dihomo-gammalinolenic acid or eicosapentaenoic acid or docosahexaenoic acid which also has anti inflammatory action.

d) Drugs used in the management of osteoporosis may be linked to GLA or DGLA which enhance the incorporation of calcium into bone, or to EPA or DHA which reduce urinary calcium excretion.

e) Drugs used in skin disease may be linked to GLA or DGLA which have anti inflammatory effects on the skin.

f) Drugs used in cancer may be linked to GLA, DGLA, arachidonic acid, EPA or DHA which have anticancer effects in their own right and which may reverse resistance to anticancer drugs.

Concepts Applied to Essential Fatty Acids as Bioactives

The essential fatty acids (EFAs) as already referred to, and well known, consist of a series of twelve compounds. Although linoleic acid, the parent compound of the n-6 series, and alpha-linolenic acid, the parent compound of the n-3 series, are the main dietary EFAS, these substances as such have relatively minor roles in the body. In order to be fully useful to the

body, the parent compounds must be metabolised to longer chain and more highly unsaturated compounds. In quantitative terms, as judged by their levels in cell membranes and in other lipid reactions dihomogammalinolenic acid (DGLA) and arachidonic acid (AA) are the main EFA metabolites of the n-6 series while eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are the main metabolites of the n-3 series. DGLA, AA, EPA and DHA are important constituents of most of the lipids in the body. As well as being important in themselves they can also give rise to a wide range of oxygenated derivatives, the eicosanoids, including the prostaglandins, leukotrienes and other compounds. The fatty acids likely to be of particular value in therapy are DGLA, AA, EPA and DHA, together with GLA, the precursor of DGLA, stearidonic acid (SA), the precursor of EPA, and DPA (22:5n3), the precursor of DHA, and adrenic acid.

Further there are fatty acids such as oleic acid, parinaric acid and columbinic acid that are not EFAs but may have significant effects in the body. One of the most interesting of these is conjugated linoleic acid which as noted earlier has a range of desirable effects.

It used to be thought that, both in nutrition and in therapy of disease, it was sufficient to supply linoleic and alpha-linolenic acids and the body's own metabolism would do the rest. It is now widely accepted that this is not true. Different diseases may have different abnormal patterns of EFAs and because of problems in metabolism these cannot simply be corrected by giving linoleic or alpha-linolenic acid. It is therefore appropriate in many situations to provide

increased amounts of one of the other EFAs or to give two or more of the EFAs simultaneously. While the EFAs can be supplied in various forms and in various mixtures, it is convenient in both nutrition and in medical treatment to be able to supply the fatty acids as particular molecules. Equally in various situations it may be desirable to give the EFA or other fatty acid in association with an amino acid, vitamin, drug or other molecule which in itself has desirable properties.

For purposes of convenient administration of different fatty acids simultaneously or indeed of a single fatty acid in high amounts in well tolerated form, use is thus desirably made of esters of 1,2-propane diol.

The Advantages and Significance of the 1,2-Propane Diol Link

When cells are exposed to stimuli, one common mode of signalling is to activate an enzyme called phospholipase C (PLC). PLC acts on the inositol phospholipids of cell membranes to remove the phosphate and inositol moieties and to leave a glycerol molecule with fatty acids at the 1 and 2 positions. This glycerol derivative is known as diacylglycerol (DAG) and can itself play an important role in cell signalling. DAG's are known to be involved in regulating calcium signalling systems and also in activating protein kinases (PK). PKs regulate the phosphorylation of proteins, a process which can convert many proteins from an inactive to an active state. DAGs are therefore very important cell regulators.

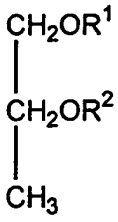
One practical problem with the synthesis of DAGs is the facile migration of an acyl group from position 2 to position 3. Thus a 1,2-diglyceride becomes a 1,3-diglyceride. Indeed further acyl migration will lead to the formation of a 2,3-diglyceride. Such migration is completely prevented by the replacement of the hydroxyl group at position 3 with a hydroben atom. Stable DAG analogues of this type are thus 3-deoxy-1,2-diglycerides (alternatively named as diesters of 1.2-propane diol).

In regard to 1,2-propane diol esters Lin and Shaw JAOCS vol. 73 no. 11 (1995) p.1271 etc. discuss the EPA and DHA monoesters as potentially health beneficial emulsifiers in the food industry and Gattefossé catalogue has offered the palmitostearate and isostearate monoesters.

The Present Invention

The present invention covers fatty acid derivatives of bioactives with an available carboxyl, alcohol or amino group such that a single, well defined chemical entity is formed. The two molecules are linked via a 1,2-propane diol link group. For bioactives with an available alcohol or amino group, a difunctional intermediate linking group (e.g. succinate) is used as a means for attachment to the 1,2-propane diol residue.

Thus, the invention relates to compounds of the following 1,2-propane diol linked structure *per se* and when for use in therapy,

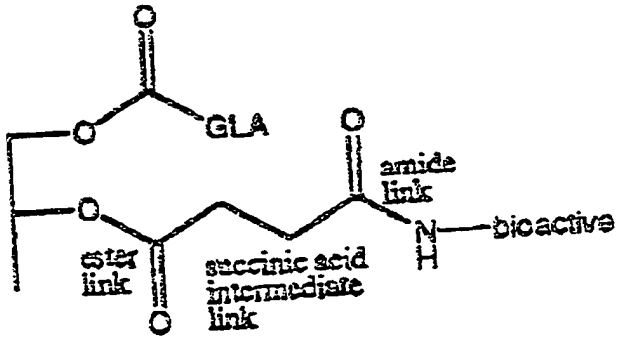


wherein R^1 or R^2 comprise an acyl group derived from a C_{12}-C_{30} preferably C_{16}-C_{30} fatty acid, desirably with two or more *cis* or *trans* double bonds, or any other nutrient, drug or other bioactive residue (which may be derivatised with a suitable intermediate linking group), such that at least one of R^1 or R^2 comprises an acyl group as defined above, and, wherein both R^1 and R^2 comprise acyl groups, they may be the same or different.

Furthermore, the present invention covers esters of both racemic and optically active 1,2-propane diol. Esters of the latter type may have either (R) or (S) configuration at C-2 of the diol backbone.

The compounds will generally be acid-function bearing actives esterified directly to the diol residue but a phosphate, succinate or other difunctional acid group may be interposed between the R^1 and/or R^2 group and the 1,2-propane diol residue particularly when R^1 and R^2 is a nutrient, drug or other bioactive having an hydroxy or amino functon., Where the nutrient, drug or other bioactive has an amino function, the difunctional group is particularly important as a means for attachment to the 1,2-propane diol residue.

The amide linkage is between the bioactive with a free amino group and an intermediate difunctional link. The other end of this difunctional link is attached to the 1,2-propane diol via an ester bond. The ideal intermediate link group for this is succinic acid. This is illustrated below, when it will be evident further that the amide link could be replaced by an ester link for example that of a fatty alcohol.



The fatty acids likely to be of most value in this context are the essential fatty acids shown in Figure 1 and, in particular, GLA, DGLA, AA, SA, EPA and DHA. For particular processes conjugated linoleic acid and columbinic acid may be of great interest.
Other aspects of the invention are set out in the claims herein.

The invention is also discussed broadly below, concerning a wide range of actives releasable in the body.

As a compound, the diol is, broadly, disclosed in the literature among many other diols but its use in therapy in the form of an essential fatty acid diester or as a compound with an essential fatty acid at one position and a bioactive (not being an essential fatty acid) at the other, is both undisclosed and particularly significant. Indeed it offers a favourable way to give a single fatty acid as the diester, Further, apart from administering individual acids, such diesters may have value in pharmaceutical formulation as emulsifiers. The 1,2-propane diol structure is close to the glycerol of natural di- and tri glycerides and an effective and safe delivery system.

Furthermore, as far as we are aware, all of the 1,2-propane diol derived compounds set out as "Examples of Pairs of Actives which may be linked via a 1,2-Propane Diol Link" below are novel compounds which have never before been described. The specific diols of two fatty acids listed and the diols where a fatty acid drawn from the list of GLA, DGLA, AA, SA, EPA, DHA, cLA and CA is present at one position and at the other position is a vitamin, amino acid, aromatic acid, steroid, antioxidant or other therapeutic drug, are new substances.

The fatty acid diesters have a wide variety of possible uses. They may be used as pharmaceuticals for the treatment of or prevention of diseases in which abnormalities of fatty acids have been identified. They may be added to foods or added to or used as nutritional supplements for those who require the particular fatty acid for the treatment or prevention of diseases. They may also be used in foods or pharmaceuticals for veterinary use. They may further be used for skin care.

As advantages or in various particular aspects including those currently in the claims herein, the invention provides:

(i) A safe and convenient way of administering, for therapeutic or nutritional purposes, two unsaturated fatty acid moieties (the same or different), or one unsaturated fatty acid and one bioactive that is not a fatty acid.

(ii) A derivative of a bioactive required to cross lipid membranes in the body to exert its action whether in entry to a cell or in passing the skin, blood-brain or other barrier, through a 1,2-propane diol linkage to an essential fatty acid on the n-6 or n-3 series and especially GLA or DGLA, AA, SA, EPA or DHA or the related fatty acids cLA or CA.

(iii) A fatty acid derivative of a drug such that the drug and fatty acid are mutually efficacious.

(iv) A method for improving the transport of a drug across lipid membranes in the body, characterised by the administration of the drug in a form as above.

(v) A method of manufacture of a medicament for improved therapy involving transport of a drug across lipid membranes in the body, characterised by incorporating the drug in a medicament in a form as above.

(vi) A method of manufacture of a medicament for delivering one or two fatty acids from the list in (ii) above or for delivering one of those fatty acids in association with another active agent.

Examples of Pairs of Actives which may be linked via a 1,2-Propane Diol link

Examples of pairs of actives follow, the resulting compounds listed being, to our knowledge novel. So far as that is so, they represent part of the invention as new chemical entities, as well as being novel in use in treatment or prevention of disease.

Fatty Acids

GLA-OA (OA = Oleic Acid), GLA-GLA, EPA-EPA, GLA-EPA, GLA-DHA, AA-DHA, AA-EPA, GLA-AA, GLA-SA, SA-DHA, AA-SA, DGLA-DGLA, DGLA-GLA, DGLA-SA, DGLA-AA, DGLA-EPA, DGLA-DHA, AA-AA, EPA-SA, EPA-DHA, DHA-DHA, cLA-cLA, c-LA-GLA, c-LA-DGLA, c-LA-AA, c-LA-SA, c-LA-EPA, c-LA-DHA, CA-CA, CA-GLA, CA-DGLA, CA-AA, CA-SA, CA-EPA, CA-DHA.

Vitamins

GLA-niacin, GLA-retinoic acid, GLA-retinol, GLA-pyridoxal, di-GLA-pyridoxine, di-EPA-pyridoxal and in general any of e.g. GLA, DGLA, AA, SA, EPA or DHA with any vitamin including ascorbic acid, Vitamin D and its derivatives and analogues, Vitamin E and its derivatives and analogues, Vitamin K and its derivatives and analogues, Vitamin B,

(thiamin), Vitamin B2 (riboflavin), folic acid and related pterins, Vitamin B12, biotin and pantothenic acid.

Amino acids

GLA-tryptophan, GLA-proline, GLA-arginine, GLA- or DHA-phenylalanine GLA-GABA, GLA-aminolevulinic acid and in general any of e.g. GLA, DGLA, AA, SA, EPA or DHA with any natural amino acid or related compound such as tarurine and carnitine.

Aromatic acids

GLA-phenylbutyric acid, GLA-phenylacetic acid, GLA-trans-cinnamic acid and in general any of e.g. GLA, DGLA, AA, SA, EPA or DHA with any aryl alkanoic or aryl alkenoic acid.

Steroids

GLA -hydrocortisone, GLA-oestradiol, GLA - and DHA-dehydroepiandrosterone and in general any of e.g. GLA, DGLA, AA, SA, EPA or DHA with any natural or synthetic steroid, such as any oestrogen, any progestin, any adrenal steroid and any anti-inflammatory steroid, particularly betamethasone, prednisone, prednisolone, triamcinolone, budesonide, clobetasol, beclomethasone and other related steroids.

Anti-oxidants

GLA-lipoic acid, DHA-lipoic acid, GLA-tocopherol, di-GLA-3,3'-thiodipropionic acid and in general any of e.g. GLA, DGLA, AA, SA, EPA or DHA with any natural or synthetic anti-oxidant with which they can be chemically linked. These include phenolic antioxidants (e.g. eugenol, carnosic acid, caffeic acid, BHT, gallic acid, tocopherols, tocotrienols and flavonoid anti-oxidants (e.g. myricetin, fisetin)), polyenes (e.g. retinoic acid), unsaturated

sterols (e.g. delta-5-avenosterol), organosulfur compounds (e.g. allicin), terpenes (e.g. geraniol, abietic acid) and amino acid antioxidants (e.g. cysteine, carnosine) .

Drugs

GLA and indomethacin, ibuprofen, fluoxetine, ampicillin, penicillin V, sulindac, salicylic acid, metronidazole, fluphenazine, dapsone, tranylcypromine, acetyl carnitine, haloperidol, mepacrine, chloroquine, penicillin, tetracycline, pravastatin, bisphosphonates such as efidronic acid, pamidronic acid and clordronic acid and their sodium salts, adenosylosuccinate and adenylosuccinate and related compounds and agents used as x-ray contrast media, and in general any of e.g. GLA, DGLA, AA, SA, EPA or DHA with any drug, particularly any drug used in the treatment of infections, inflammatory diseases, including various forms of arthritis, cancer, cardiovascular, respiratory, dermatological, psychiatric, neurological, muscular, renal, gastrointestinal, reproductive and other diseases.

Uses Generally

Particular uses of particular groups of compounds are indicated elsewhere herein. The usefulness and advantages, generally, of the 1,2-propane diol esters include the following:

1 . Improved tolerability of fatty acids. Apart from the triglycerides, most forms in which fatty acids can be administered including free acids, salts, ethyl esters and other glycerides cause some degree of gastrointestinal intolerance as shown by nausea, vomiting and diarrhoea.

2. Reduced toxicity of drugs. The non-steroidal anti-inflammatory drugs such as aspirin and indomethacin are notorious for causing severe gastointestinal toxicity with ulceration of the stomach and intestines and bleeding into the gastointestinal tract.

3. Efficient delivery of a biologically active form of the fatty acid.

The fatty acids themselves have a large number of desirable biological and therapeutic activities which have been detailed in numerous publications by the inventors and by others. Four of the fatty acids, GLA, DGLA, SA and EPA share a rather broad spectrum of effects which include:

1 . Cardiovascular actions including vasodilatation, lowering of blood pressure inhibition of platelet aggregation, lowering of triglyceride and LDL-cholesterol levels; elevation of HDL-cholesterol levels and inhibition of smooth muscle proliferation.

2. Anti-inflammatory actions including reduction of formation of pro-inflammatory mediators such as cytokines, and of eicosanoids derived from arachidonic acid, reduction of neutrophil migration and the neutrophil respiratory burst, reduction of local inflammatory responses, inhibition of inflammation in various animal models such as uric acid induced inflammation and adjuvant arthritis, and treatment of various inflammatory disorders such as osteoarthritis and rheumatoid arthritis.

3. Immunomodulatory functions including the damping down of excessive immune and allergic responses in animal models such as experimental allergic encephalomyelitis and uveitis, bronchial and cutaneous hyper-reactivity in sensitised animals, leading to the concept that they are of value in human diseases where excessive immune responses play a role.

4. Respiratory actions including bronchodilatation and inhibition of bronchoconstrictor actions.

5. Improvements in calcium balance with increased calcium absorption, reduced calcium excretion, increased deposition of calcium in bones and reduced ectopic deposition of calcium in tissues such as arteries and kidneys.

6. Anticancer effects of three sorts, selective cytotoxic damage and induction of apoptosis in cancer cells but not in normal cells, inhibition of growth by reduction of action of growth factors and interference with second messenger systems required for growth, inhibition of metastasis by various actions including increased expression of E-cadherins and inhibition of proteolytic enzymes such as urokinases, lipoxygenase and matrix metalloproteinases, and inhibition of cancer-associated cachexia.

7. Actions on nerve cells including maintenance of normal nerve membrane structure and function and the normal pre- and post-synaptic actions of neurotransmitters.

These desirable actions mean that this group of fatty acids can be used in the treatment of many different disorders including cardiovascular disorders of many types, inflammatory disorders including rheumatoid arthritis, osteoarthritis, ulcerative colitis and Crohn's disease, respiratory disorders including asthma, psychiatric disorders including schizophrenia, alcoholism, attention deficit disorder, depression and Alzheimer's disease, neurological disorders including multiple sclerosis and Huntington's chorea, renal and urinary tract disorders including various types of renal inflammatory disease and urinary calcium stones, metabolic disorders including osteoporosis and ectopic calcification, and gastrointestinal ulcerative and inflammatory diseases. Although conjugated linoleic acid (cLA) has not been nearly as widely tested as, say GLA or EPA, it also seems to have a wide range of actions including effects valuable in the treatment of cancer, cardiovascular and metabolic diseases.

GLA, DGLA, AA and columbinic acid have desirable actions on the skin and are particularly valuable in the treatment of skin diseases such as atopic eczema, psoriasis, urticaria and allergic reactions.

AA is often regarded as a potentially harmful fatty acid. However, it is an essential constituent of all normal cell membranes and has been found to be present in low levels in various illnesses including atopic eczema, schizophrenia (Horrobin et al, Schizophrenia Res.

1994; 13: 195-207) and cardiovascular disorders (Horrobin, Prostaglandins Leukotr. EFAs 1995; 53: 385-96). AA is likely to be of particular value in these situations and also in other psychiatric disorders such as alcoholism and attention deficit disorder where levels are also often low.

DHA shares some of the above actions of the EFAs but is found in particularly important amounts in cell membranes and especially in the membranes of the heart, the retina and the brain. DHA also has potent anti-inflammatory and desirable cardiovascular effects. DHA is likely to be of particular value in cardiovascular disorders, in retinal and visual disorders including retinitis pigmentosa, senile macular degeneration and dyslexia, and in psychiatric and neurological disorders including schizophrenia, attention deficit disorder, depression, alcoholism, Alzheimer's disease and other forms of dementia and multiple sclerosis.

Infections have also recently been identified as likely to respond to fatty acids, especially to GLA and DGLA, EPA and DHA. Many bacteria are killed by these fatty acids, including strains which are highly resistant to antibiotics. Recent work from a number of laboratories has also shown that these highly unsaturated fatty acids are important in successful responses to diseases like malaria and to protozoal diseases.

It is thus apparent that various specific fatty acids are likely to be able to add to the efficacy of drugs and other bioactive substances of almost any class, in both the treatment and prevention of disease, in skin care and in nutrition, as well as having valuable therapeutic effects when given in the diol form as a single fatty acid or as two different fatty acids in the same molecule. Of particular value in therapy is that under most circumstances the fatty acids are remarkably non-toxic and can be administered safely in large doses without the risk of important side effects.

Specific uses of particular 1,2-propane diol compounds

1. 1,2-propane diol as derivatives containing: two fatty acids in which one fatty acid is GLA or DGLA and the other is GLA, DGLA, SA, EPA, DHA, cLA (conjugated linoleic acid) or CA (columbinic acid) for the treatment of

(a) complications of diabetes, particularly neuropathy and retinopathy; and improvement of responses to insulin in diabetes and pre-diabetes;

(b) cancers;

(c) osteoarthritis;

(d) rheumatoid arthritis;

(e) other inflammatory and auto-immune diseases including Sjogren's syndrome, systemic lupus, ulcerative colitis, Crohn's disease and uveitis;

(f) respiratory diseases including asthma;

(g) neurological disorders including multiple sclerosis, Parkinson's disease and Huntington's chorea;

(h) renal and urinary tract disorders;

(i) cardiovascular disorders;

(j) degenerative of the eye including retinitis pigmentosa and senile macular degeneration;

(k) psychiatric disorders including schizophrenia, Alzheimer's disease, attention deficit disorder, alcoholism and depression;

(l) prostatic hypertrophy and prostatitis;

(m) impotence and male infertility;

(n) mastalgia;

(o) male pattern baldness;

(p) osteoporosis;

(q) dermatological disorders, including atopic eczema, hand eczema, psoriasis, urticaria and allergic disorders;

(r) dyslexia and other learning disabilities;

(s) cancer cachexia.

2. 1,2-propane diol as derivatives containing two fatty acids in which one fatty acid is AA and the other is AA, GLA, DHA, DGLA or EPA for treatment of the disorders as at (1) above and especially (a), (g), (i),(j), (k), (q) and (r).

3. 1,2-propane diol as derivatives containing two fatty acids in which one fatty acid is EPA and the other is EPA or DHA for the treatment of any of the disorders as at (1) above but especially (b), (c), (d), (e), (f), (g), (h), (i), j), (k), (p), (r) and (s).

4. 1,2-propane diol as derivatives in which one position is occupied by a fatty acid drawn from GLA, DGLA, AA, SA, cLA, EPA or DHA and the other position is occupied by an agent, selected from the following list, whose chemical structure is such that it can be linked to the 1,2-propane diol by one of the linkages described herein:

(a) tryptophan for the treatment of any disease but particularly for psychiatric neurological, behavioural, pain and other disorders and especially depression, sleep and migraine;

(b) phenylalanine for the treatment of any disease, but especially depression, multiple sclerosis and chronic fatigue syndrome;

(c) arginine for the treatment of any disease but particularly diseases in which the production of nitric oxide is defective;

(d) carnitine or caoritine derivatives for the treatment of any disease but especially muscle weakness, cardiac failure, chronic fatigue syndrome, Alzheimer's disease, and peripheral neuropathies;

(e) any other amino acid or related substance for the treatment of any disease or aminolevulinic acid or derivative thereof for the treatment of any disease but especially cancers;

(f) adenylosuccinate or related substances for the treatment of any disease but especially muscular dystrophy, cardiac failure, chronic fatigue and Alzheimer's disease and other dementias;

(g) aspirin, salicylic acid, indomethacin, ibuprofen, or any other non-steroidal anti-inflammatory drug for the treatment of any disease but especially of inflammatory disorders, of pain, of Alzheimer's disease and other dementias and of any disease in which platelet aggregation should be inhibited;

(h) any antibiotic for the treatment of any appropriate infectious disease but especially tetracycline, clindamycin, minocycline, chlortetracycline and erythromycin for the treatment of acne;

(i) any anti-malarial or anti-protozoal drug for the treatment of any disease, but especially chloroquine, mepacrine, quinacrine and mefloquine for the treatment of malaria, protozoal disorders, inflammatory disorders and schizophrenia;

(j) any antifungal drug for the treatment of any disease but especially metronidazole and antifungal imidazoles and nitroimidazoles and amphotericin for the treatment of fungal infections of various types;

(k) any anti-inflammatory steroid for the treatment of any disease but especially hydrocortisone and betamethasone for the treatment of skin disorders and beclomethasone and budesonide for the treatment of asthma.

(l) any gonadal steroid for the treatment of any disease but especially oestrogens and progestogens for the treatment of ovarian deficiency and osteoporosis and androgens for the treatment of testicular deficiency;

(m) any adrenal steroid for the treatment of any disease, but especially dehydroepiandrosterone for the treatment of disorders associated with ageing;

(n) any retinoid for the treatment of any disease but especially tretinoin and isotretinoin for the treatment of dermatological disorders and for use in skin care;

(o) any anticancer agent for the treatment of cancer;

(p) any antipsychotic agent for the treatment of schizophrenia and other psychoses;

(q) any antidepressive agent for the treatment of any disease but especially for the treatment of depression;

(r) any anti-anxiety agent for the treatment of any disease, but especially for the treatment of anxiety and panic attacks;

(s) any immunosuppressive agent for the treatment of any disease but especially cyclosporine and tacrolimus for the control of immunity after organ transplantation and for the treatment of autoimmune and inflammatory disorders including psoriasis, eczema, asthma, rheumatoid arthritis and inflammatory bowel disease;

(t) any proton pump inhibitor or H2 antagonist for the treatment of any disease but especially diseases associated with excess gastric acid production or reduced defences against gastric acidity;

(u) any diuretic for any disease, but especially for diseases associated with fluid retention and hypertension;

(v) any calcium antagonist used for any disease but especially for cardiovascular diseases;

(w) any angiotensin converting-enzyme inhibitor or angiotensin antagonist used for any disease but especially for cardiovascular diseases;

(x) any beta-blocker used for any disease but especially for cardiovascular disorders;

(y) any antiepileptic drug used for any disease, but especially phenytoin, carbamazepine, valproate, ethosuximide, vigabatrin or lamotrigine for the treatment of epilepsy;

(z) any hypolipidaemic agent for the treatment of any disease but especially fibrates and statins used for cholesterol lowering and cholesterol modification;

(aa) any oral hypoglycaemic or insulin-sensitising agents used in the management of diabetes;

(bb) any bisphosphonates used in the management of osteoporosis, Paget's disease or cancer;

(cc) any contrast agents used in radiology including diatrizoate compounds iodipamide, ioglycamates, iopanoates, iophendylate, iothalamate, ioxaglate, metrizamide and related compounds;

(dd) any peptide or protein for use in the treatment of diseases for which the peptide or protein itself is used, including insulin, calcitonin, erythropoietin and other peptides ;

(ee) any vitamin used in the treatment of any disease, or used in foods, nutritional supplements or food additives as a way of providing the vitamin effectively,

(ff) any antioxidant used in the management of any disease, but especially for those diseases in which antioxidants may be especially beneficial including cardiovascular diseases, cancer and inflammatory disorders and any antioxidant used as a food or other preservative or as a component of a food, food additive or nutritional supplement,

gg) any porphyrin chlorin or bacteriochlorin-based drug especially tetrakis (hydroxy phenyl) derivatives thereof used in photodynamic therapy of cancers.

The present invention covers esters of both racemic and optically active 1,2-propane diol. There are a number of methods in the published literature for the synthesis of optically active compounds which may be appropriate for the preparation of these compounds.

These include, but are not limited to:

(a) synthesis from naturally occurring chiral pool materials (e.g. lactic acid)

(b) asymmetric chemical synthesis (e.g. Sharpless asymmetric epoxidation)

(c) kinetic resolution (e.g. hydrolase mediated esterification or hydrolysis)

Derivatisation of an unsaturated fatty acid (UFA) or a bioactive having a free carboxyl group requires the formation of an ester bond.

Derivatisation of a bioactive having a free hydroxyl group requires the formation of either a carboxylic ester bond or a phosphate ester bond.

Derivatisation of a bioactive having a free amine group requires the formation of an amide bond.

Formation of an ester bond may be achieved by any reasonable method for such chemistry and especially:

(d) by reaction of alcohol with acid chloride, acid anhydride or suitably activated ester, with or without the presence of an organic tertiary base, e.g. pyridine, in a suitable inert solvent, e.g. dichloromethane, at a temperature between 0° and 120°C.

(e) by reaction of alcohol with acid or acid, short or medium chain alkyl ester, in the presence of a suitable acid catalyst, e.g. *para*-toluene sulphonic acid, with or without a suitable inert solvent, e.g. toluene, at a temperature between 50° and 180°C such that the water formed in the reaction is removed, e.g. under vacuum.

(f) by reaction of alcohol with acid in the presence of a condensing agent, e.g. 1,3-dicyclohexylcarbodiimide, with or without the presence of a suitable organic tertiary base, e.g. 4-(N,N-dimethylamino)pyridine, in an inert solvent, e.g. dichloromethane, at a temperature between 0° and 50°C.

(g) by reaction of alcohol with acid or acid, short or medium chain alkyl ester, or acid, activated ester, e.g. vinyl, in the presence of a hydrolase enzyme, e.g. hog liver esterase, with or without a suitable solvent, e.g. hexane, at temperatures between 20° and 80°C under conditions such that the water or alcohol or aldehyde by-product is removed, e.g. under vacuum.

(h) by reaction of a suitable alcohol derivative, e.g. iodide, with acid, with or without the presence of a suitable base, e.g. potassium carbonate, in an inert solvent, e.g. dimethylformamide, at a temperature between 0° and 180°C.

(i) by reaction of alcohol with acid, short or medium chain alkyl ester, in the presence of a catalytic amount of an alkoxide of type M^+OY^- where M is an alkali or alkaline earth metal, e.g. sodium, and Y is an alkyl group containing 1-4 carbon atoms which may be branched, unbranched, saturated or unsaturated, with or without the presence of a suitable solvent,

e.g. toluene, at a temperature between 50° and 180°C such that the lower alcohol, HOY, is removed from the reaction mixture, e.g. under vacuum.

Formation of an amide bond may be achieved by any reasonable method for such chemistry and especially:

(j) by reaction of amine with acid chloride, acid anhydride or suitably activated ester with or without the presence of an organic tertiary base, e.g. pyridine, in a suitable inert solvent, e.g. dichloromethane, at a temperature between 0° and 120°C.

(k) by reaction of amine with acid in the presence of a condensing agent, e.g. 1,3-dicyclohexylcarbodiimide, with or without the presence of a suitable organic tertiary base, e.g. 4-(N,N-dimethylamino)pyridine, in an inert solvent, e.g. dichloromethane, at a temperature between 0° and 50°C.

(l) by reaction of amine with acid or acid, short or medium chain alkyl ester, or acid, activated ester, e.g. vinyl, in the presence of a hydrolase enzyme, e.g. hog liver esterase, with or without a suitable solvent, e.g. hexane, at a temperature between 20° and 80°C under conditions such that the water or alcohol or aldehyde by-product is removed, e.g. under vacuum.

Formation of a phosphate ester bond may be achieved by any reasonable method for such chemistry and especially:

(m) by reaction of alcohol, e.g. UFA 1,2-propane diol monoester, with a suitably activated phosphate derivative, e.g. phosphorus oxychloride, with a tertiary base, e.g. triethylamine, in a suitable solvent, e.g. tetrahydrofuran, at a temperature between -20° and 20°C, to yield crude phosphorodichloridate.This is followed by reaction of alcohol, e.g. α-tocopherol, with the crude phosphorodichloridate with a tertiary base, e.g. triethylamine, in a suitable solvent, e.g. tetrahydrofuran, at a temperature between 0° and 50°C, to yield crude phosphorochloridate. This may be hydrolysed, e.g. by addition of water and triethylamine, to yield phosphodiester. Alternatively, addition of methanol yields a phosphotriester which may be demethylated using a suitable nucleophile, e.g. lithium bromide, in a suitable solvent, e.g. methyl ethyl ketone, to yield the phosphodiester.

(n) by reaction of phosphomonoester, e.g. UFA 1,2-propane diol monoester phosphate, with alcohol, e.g. choline, in the presence of a condensing agent, e.g. 1,3-dicyclohexylcarbodiimide, in a suitable solvent at a temperature between 0° and 120°C.

The individual fatty acids may be purified from natural animal, vegetable or microbial sources or may be chemically synthesised by methods known to those skilled in the art or developed hereafter. Likewise the individual fatty alcohols may be prepared by reduction of the fatty acid, by known methods or newly developed ones.

Formulations

The compounds may be formulated in any way appropriate and which is known to those skilled in the art of preparing pharmaceuticals, skin care products or foods. They may be administered orally, enterally, topically, parenterally (subcutaneously, intramuscularly, intravenously), rectally, vaginally or by any other appropriate route.

Like triglycerides, the 1,2-propane diol diesters, especially those containing two fatty acids, may be readily emulsified using phospholipid or particularly galactolipid emulsifiers. Such emulsions are particularly useful for administration via oral, enteral and intravenous routes.

For example, fatty acid (UFA) diesters occur as free flowing oils and therefore can be formulated as follows:-

1. Preparation of 20 % Emulsion of Diester of GLA and EPA with 1,2-propane diol

Oral emulsions were prepared by high-pressure homogenisation. The particle size distributions and the zeta potential of the resulting emulsions were determined by dynamic light scattering at room temperature. The particle size measurements were carried out at room temperature (Zetasizer 4 Malvern Instruments Limited).

An oil-in-water emulsion (batch size 200g) was prepared containing the following ingredients:-

Ingredients	%
Emulsifier (Galactolipid)[1]	2.00
Diester (GLA-EPA)	20.00
Ascorbyl Palmitate (AP)	0.02
Vitamin E	0.5
Water add to	100.00

The emulsifier-galactolipid, as disclosed in Scotia Lipidteknik patent PCT SE95/00115 (WO 95/20943), was dispersed in the diester and, Vitamin E, AP and water were mixed. The oil phase was added to the aqueous phase under a high shear mix (Ultraturrax) at speed 4, for a few minutes. This pre-emulsion was then homogenised at 80 MPA and at 50'C for 6 cycles (mini-Lab 8.30 H; APV Rannie AS, Demnark). The emulsion formed has an average droplet size of 230 nm.

Anti-microbial preservatives - potassium sorbate, and flavour, can also be added to the above oral emulsion.

2. Preparation of Intravenous 20% Emulsion of Diester of GLA and EPA with 1,2- propane diol.

In a similar manner, 200g of an oil-in-water emulsion was prepared containing the following ingredients:-

Ingredients	%
Emulsifier	2.0
Diester 9GLA-EPA)	20.0
Glycerol	2.0
Water add to	100.00

The above emulsion, homeginised for 6 minutes in a high pressure homogeniser had an average droplet size of 211 nm, a zeta potential of -40mV. These I.V.emulsions can be either filtered through a membrane with a pore size of 0.22 microns or can be autoclaved with change in droplet size.

The doses of the actives to be administered largely range from 1mg to 200g per day, preferably 10mg to 10g and very preferably 10mg to 3g, according to their kind. In the treatment of cancer preferable doses may be in the 2-150g/day range. They may be

administered topically where appropriate in preparations where the actives form from 0.001% to 50% of the topical preparation, preferably 0.05% and very preferably 0.1% to 10%.

Synthesis examples

The following use GLA and AA as n-6 essential fatty acids and DHA and EPA as n-3 essential fatty acids but exactly comparable methods are suited to the other fatty acids described and claimed.

Example 1

(±)-1,2-di(*z,z,z*-octadeca-6,9,12-trienoyloxy)propane
(Racemic diester of GLA with 1,2-propane diol)

A mixture of (±)-1,2-propane diol (6.85g), *z,z,z*-octadeca-6,9,12-trienoic acid (50g) and immobilised lipase enzyme (5g) was heated at 60°C under vacuum (*ca.* 200mmHg) with a vigorous nitrogen purge for 5h. Tlc analysis indicated almost complete reaction. The reaction mixture was cooled, diluted with hexane, filtered, concentrated and purified by silica gel chromatography to yield (±)-1,2-di(*z,z,z*-octadeca-6,9,12-trienoyloxy)propane as a yellow oil.

Example 2

(±)-1,2-di(*z,z,z,z,z,z*-docosa-4,7,10,13,16,19-hexaenoyloxy)propane
(Racemic diester of DHA with 1,2-propane diol)

In a similar manner to Example 1 but replacing *z,z,z*-octadeca-6,9,12-trienoic acid with *z,z,z,z,z,z*-docosa-4,7,10,13,16,19-hexaenoic acid was prepared (±)-1,2-di(*z,z,z,z,z,z*-docosa-4,7,10,13,16,19-hexaenoyloxy)propane as a pale yellow oil.

Example 3

(±)-1,2-di(*z,z,z,z*-eicosa-5,8,11,14-tetraenoyloxy)propane
(Racemic diester of AA with 1,2-propane diol)

In a similar manner to Example 1 but replacing *z,z,z*-octadeca-6,9,12-trienoic acid with *z,z,z,z*-eicosa-5,8,11,14-tetraenoic acid was prepared (±)-1,2-di(*z,z,z,z*-eicosa-5,8,11,14-tetraenoyloxy)propane as a pale yellow oil.

Example 4

(±)-1,2-di(*z,z,z,z,z*-eicosa-5,8,11,14,17-pentaenoyloxy)propane
(Racemic diester of EPA with 1,2-propane diol)

A solution of *z,z,z,z,z*-eicosa-5,8,11,14,17-pentaenoyl chloride (2g) (prepared by reaction of *z,z,z,z,z*-eicosa-5,8,11,14,17-pentaenoic acid with oxalyl chloride in hexane) in dichloromethane (5mL) was added to a mixture of (±)-1,2-propane diol (230mg) and triethylamine (1.05mL) in dichloromethane (10mL) at room temperature under nitrogen. After stirring for 1h, the reaction mixture was allowed to stand overnight under nitrogen. Tlc analysis indicated essentially complete reaction. The reaction mixture was diluted with hexane, filtered, concentrated and purified by silica gel chromatography to yield (±)-1,2-di(*z,z,z,z,z*-eicosa-5,8,11,14,17-pentaenoyloxy)propane as a pale yellow oil.

Example 5

1,2(R)-di(*z,z,z*-octadeca-6,9,12-trienoyloxy)propane
(Enantiopure diester of GLA with 1,2-propane diol)

A mixture of 1,2(R)-propane diol (500mg), *z,z,z*-octadeca-6,9,12-trienoic acid (3.66g), 1,3-dicyclohexylcarbodiimide (2.85g) and 4-(N,N-dimethylamino)pyridine (1.69g) in dichloromethane (20mL) was stirred overnight under nitrogen at room temperature. The reaction mixture was filtered through Celite, concentrated and purified by silica gel chromatography to yield 1,2(R)-di(*z,z,z*-octadeca-6,9,12-trienoyloxy)propane as a colourless oil.

Example 6

1,2(S)-di(*z,z,z*-octadeca-6,9,12-trienoyloxy)propane
(Enantiopure diester of GLA with 1,2-propane diol)

In a similar manner to Example 5 but replacing 1,2(R)-propane diol with 1,2(S)-propane diol was prepared 1,2(S)-di(*z,z,z*-octadeca-6,9,12-trienoyloxy)propane
as an almost colourless oil.

Example 7

(±)-1-(*z,z,z*-octadeca-6,9,12-trienoyloxy)-2-(*z,z,z,z,z*-eicosa-5,8,11,14,17-pentaenoyloxy)propane and (±)-1-(*z,z,z,z,z*-eicosa-5,8,11,14,17-pentaenoyloxy)-2-(*z,z,z*-octadeca-6,9,12-trienoyloxy)propane.
(Racemic diester of GLA and EPA with 1,2-propane diol - mixture of positional isomers).

Part 1- (±)-1-(*z,z,z*-octadeca-6,9,12-trienoyloxy)propan-2-ol and (±)-2-(*z,z,z*-octadeca-6,9,12-trienoyloxy)propan-1-ol

A mixture of (±)-1,2-propane diol (102.7g), *z,z,z*-octadeca-6,9,12-trienoic acid (75g) and Amberlyst-15 (trade mark) ion exchange resin (3.75g) was heated at 100°C under vacuum (*ca.* 200mmHg) with a vigorous nitrogen purge. Tlc analysis after 8h indicated some unreacted fatty acid. Heating under the same conditions was continued for another 4h, at which point tlc analysis indicated essentially complete reaction. After cooling the reaction mixture to room temperature, unreacted 1,2-propane diol was removed by distillation under reduced pressure. The residual oil was filtered to remove Amberlyst-15, diluted with diethyl ether (600mL) and washed with water (2x750mL). The organic layer was dried (magnesium sulfate) and concentrated under reduced pressure. The residual oil was dissolved in acetonitrile (250mL) and extracted with 2,2,4-trimethylpentane (3x100mL). The acetonitrile solution was concentrated to dryness, redissolved in ethyl acetate(250mL), washed with water (250mL) and dilute brine (250mL), dried (magnesium sulfate) and concentrated under reduced pressure to leave a mixture of 1- and 2- monoesters as a yellow oil.

Part 2 - (±)-1-(*z,z,z*-octadeca-6,9,12-trienoyloxy)-2-(*z,z,z,z,z*-eicosa-5,8,11,14,17-pentaenoyloxy)propane and (±)-1-(*z,z,z,z,z*-eicosa-5,8,11,14,17- pentaenoyloxy)-2-(*z,z,z*-octadeca-6,9,12-trienoyloxy)propane

A solution of *z,z,z,z,z*-eicosa-5,8,11,14,17-pentaenoic acid (4.5g) in dichloromethane (5mL) was added to a mixture of 1,3-dicyclohexylcarbodiimide (3.2g), 4-(N,N-dimethylamino)pyridine (1.9g), (±)-1-*z,z,z*-octadeca-6,9,12-trienoyloxypropan-2-ol and (±)-2-*z,z,z*-octadeca-6,9,12-trienoyloxypropan-1-ol (5g) in dichloromethane (20mL) and the resulting mixture was stirred at room temperature under nitrogen. On completion of reaction, as evidenced by tlc analysis, the reaction mixture was diluted with hexane, filtered, concentrated and purified by silica gel chromatography to yield (±)-1-(*z,z,z*-octadeca-6,9,12-trienoyloxy)-2-(*z,z,z,z,z*-eicosa-5,8,11,14,17-pentaenoyloxy)propane and (±)-1-(*z,z,z,z,z*-eicosa-5,8,11,14,17-pentaenoyloxy)-2-(*z,z,z*-octadeca-6,9,12-trienoyloxy)propane as a colourless oil.

Example 8

1-(*z,z,z,z,z*-eicosa-5,8,11,14,17-pentaenoyloxy)-2(S)-(*z,z,z,z,z,z*-docosa-4,7,10,13,16, 19-hexaenoyl)propane

(Enantiopure diester of EPA and DHA with 1,2-propane diol)

Part 1 - 2(S)-(1'-ethoxyethoxy)-1-propanol

To a stirred, cooled (0°C) solution of ethyl lactate (227mL) and ethyl vinyl ether (574mL)(freshly distilled from potassium carbonate) was added trifluoroacetic acid (4.2mL). The mixture was stirred at 0°C for 3h, refrigerated overnight, allowed to warm to room temperature and treated with triethylamine (21.8mL). Stirring was continued for 30 min. and most of the excess ethyl vinyl ether was removed under reduced pressure at room temperature. The residue was diluted with diethyl ether (800mL), washed with water (800mL), brine (400mL), dried (magnesium sulfate and potassium carbonate) and concentrated under reduced pressure (bath temp. = 30°C) to yield 2(S)-(1'-ethoxyethoxy)ethyl propanoate (361g) which was used without any further purification.

A solution of 2(S)-(1'-ethoxyethoxy)ethyl propanoate (137g) in diethyl ether (140mL) was added to a stirred solution of sodium bis(2-methoxyethoxy)aluminium hydride (Red-Al) (70% w/w solution in toluene; 250g) at a rate so as to maintain a slow reflux. On completion of addition, stirring was continued at room temperature for 2h. Excess reducing agent was destroyed by the dropwise addition of 50% v/v diethyl ether/ethanol (56mL). The reaction mixture was washed with sodium hydroxide solution (28%, 600mL) and brine (500mL), dried (magnesium sulfate and potassium carbonate), concentrated under reduced pressure (bath temp. = 50°C). Careful distillation yielded 2(S)-(1'-ethoxyethoxy)-1-propanol.

Part 2 - 1-(4-methylphenyl)sulfonyloxy-propan-2(S)-ol

4-(Methylphenyl)sulfonyl chloride (22.9g) was added to a stirred and cooled (5°C) solution of 2(S)-(1'-ethoxyethoxy)-1-propanol (16.2g), triethylamine (19.8mL) and 4-(N,N-dimethylamino)pyridine (1.33g) in dichloromethane (160mL) and the resulting mixture was stirred at 0-5°C for 4h. The mixture was poured into ice/water (100mL) and extracted with dichloromethane (2x40mL). The organic extracts were combined and washed with 1M hydrochloric acid (90mL) and brine (100mL), dried (magnesium sulfate) and concentrated under reduced pressure. The residual oil was dissolved in a mixture of THF (100mL), water (11mL) and 2M hydrochloric acid (4mL) at room temperature and the resulting solution stirred vigorously at room temperature for 2h. The reaction mixture was concentrated under reduced pressure to remove THF. The residue was taken up in dichloromethane (100mL) and washed with water (100mL), saturated sodium hydrogencarbonate solution (80mL) and brine (80mL), dried (magnesium sulfate) and concentrated under reduced pressure to yield 1-(4-methylphenyl)sulfonyloxy-propan-2(S)-ol as a viscous, clear yellow oil. (A sample of this oil was crystallised from ether/pentane. This yielded off-white crystals [m.p.= 33-35°C]).

Part 3 - 1-(4-methylphenyl)sulfonyloxy-2(S)-(*z,z,z,z,z,z*-docosa-4,7,10,13,16,19-hexaenoyloxy)propane.

A mixture of 1-(4-methylphenyl)sulfonyloxy-propan-2(S)-ol (2.29g), 1,3-dicyclohexylcarbodiimide (2.27g), 4-(N,N-dimethylamino)pyridine (1.34g) and *z,z,z,z,z,z*-docosa-4,7,10,13,16,19-hexaenoic acid (3.28g) in dichloromethane (20mL) was stirred at room temperature under nitrogen for 3h. The reaction mixture was filtered, washed with 1M hydrochloric acid (100mL) and 10% aqueous sodium chloride solution (3 x 100mL), dried (magnesium sulfate) and concentrated to dryness under reduced pressure.

Part 4 - 1-(*z,z,z,z,z*-eicosa-5,8,11,14,17-pentaenoyloxy)-2(S)-(*z,z,z,z,z,z*-docosa-4,7,10,13,16,19-hexaenoyl)propane

A mixture of 1-(4-methylphenyl)sulfonyloxy-2(S)-(*z,z,z,z,z,z*-docosa-4,7,10,13,16,19-hexaenoyloxy)propane (500mg), *z,z,z,z,z*-eicosa-5,8,11,14,17-pentaenoic acid (140mg) and cesium fluoride (140mg) in anhydrous DMF (5mL) was heated with stirring at 50°C under nitrogen for 3 days. After this reaction period the reaction mixture was cooled and partitioned between ethyl acetate (50mL) and saturated sodium hydrogencarbonate solution (50mL). The ethyl acetate extract was washed with brine (3x100mL), dried (magnesium sulfate) and concentrated under reduced pressure. Purification by silica gel chromatography yielded 1-(*z,z,z,z,z*-eicosa-5,8,11,14,17-pentaenoyloxy)-2(S)-(*z,z,z,z,z,z*-docosa-4,7,10,13,16, 19-hexaenoyl)propane as an orange oil.

Example 9

1-(*z,z,z*-octadeca-6,9,12-trienoyloxy)-2(S)-(*z,z,z,z*-eicosa-5,8,11,14-tetraenoyl oxy)propane and 1-(*z,z,z,z*-eicosa-5,8,11,14-tetraenoyloxy)-2(S)-(*z,z,z*-octadeca-6,9,12-trienoyloxy)propane *(Enantiopure diester of GLA and AA with 1,2-propane diol - mixture of positional isomers)*

Part 1 - 1-(*z,z,z*-octadeca-6,9,12-trienoyloxy)-2(S)-(1'-ethoxyethoxy)propane

A solution of *z,z,z*-octadeca-6,9,12-trienoic acid (5g) in dichloromethane (5mL) was added to a mixture of 1-(4-methylphenyl)sulfonyloxy-propan-2(S)-ol (prepared as in Example 8, Part 2) (2.66g), 1,3-dicyclohexylcarbodiimide (3.9g) and 4-(N,N-dimethylamino)pyridine (2.3g) in dichloromethane (20mL) and the reaction mixture was stirred at room temperature under nitrogen. When the reaction was complete as evidenced by tlc analysis, the reaction mixture was diluted with hexane (50mL) and filtered. The filtrate was concentrated under reduced pressure and purified by silica gel chromatography to yield 1-(*z,z,z*-octadeca-6,9,12-trienoyloxy)-2(S)-(1'-ethoxyethoxy) propane as a colourless oil.

Part 2 - 1-(*z,z,z*-octadeca-6,9,12-trienoyloxy)propan-2(S)-ol and 2(S)-(*z,z,z*-octadeca-6,9,12-trienoyloxy)propan-1-ol

A mixture of 1-(*z,z,z*-octadeca-6,9,12-trienoyloxy)-2(S)-(1'-ethoxyethoxy)propane (3.8g) and 2M hydrochloric acid (1.5mL) in THF (12mL) was stirred at room temperature under nitrogen for 2h. Tlc analysis at this stage indicated complete reaction. THF was removed under reduced pressure and the residue was dissolved in dichloromethane (100mL) and washed with water (50mL), saturated aqueous sodium hydrogencarbonate solution (50mL) and brine (50mL), dried (magnesium sulfate) and concentrated under reduced pressure. This yielded 1-(*z,z,z*-octadeca-6,9,12-trienoyloxy)propan-2(S)-ol and 2(S)-(*z,z,z*-octadeca-6,9,12-trienoyloxy)propan-1-ol.

Part 3 - 1-(*z,z,z*-octadeca-6,9,12-trienoyloxy)-2(S)-(*z,z,z,z*-eicosa-5,8,11,14-tetraenoyloxy)propane and 1-(*z,z,z,z*-eicosa-5,8,11,14-tetraenoyloxy)-2(S)- (*z,z,z*-octadeca-6,9,12-trienoyloxy)propane

A solution of 1,3-dicyclohexylcarbodiimide (640mg) and 4-(N,N-dimethylamino) pyridine (380mg) in dichloromethane (10mL) was added with stirring to a solution of 1-(*z,z,z*-octadeca-6,9,12-trienoyloxy)propan-2(S)-ol and 2(S)-(*z,z,z*-octadeca-6,9,12-trienoyloxy)propan-1-ol (1g) and *z,z,z,z*-eicosa-5,8,11,14-tetraenoic acid (1.08g) in dichloromethane (10mL). The resulting mixture was stirred overnight at room temperature under nitrogen. The reaction mixture was diluted with hexane, filtered, concentrated under reduced pressure and purified by silica gel chromatography to yield 1-(*z,z,z*-octadeca-6,9,12-trienoyloxy)-2(S)-(*z,z,z,z*-eicosa-5,8,11,14-tetraenoyl oxy)propane and 1-(*z,z,z,z*-eicosa-5,8,11,14-tetraenoyloxy)-2(S)-(*z,z,z*-octadeca-6,9,12-trienoyloxy)propane as an almost colourless oil.

Example 10

1-(*z,z,z*-octadeca-6,9,12-trienoyloxy)-2(S)-(*z,z,z,z,z,z*-docosa-4,7,10,13,16,19-hexaenoyloxy)propane and 1-(*z,z,z,z,z,z*-docosa-4,7,10,13,16,19-hexaenoyloxy)-2(S)-(*z,z,z*-octadeca-6,9,12-trienoyloxy)propane.
(Enantiopure diester of GLA and DHA with 1,2-propane diol - mixture of positional isomers)

In a similar manner to Example 9 but replacing *z,z,z,z*-eicosa-5,8,11,14-tetraenoic acid in Part 3 with *z,z,z,z,z,z*-docosa-4,7,10,13,16,19-hexaenoic acid yielded 1-(*z,z,z*-octadeca-6,9,12-trienoyloxy)-2(S)-(*z,z,z,z,z,z*-docosa-4,7,10,13,16,19-hexaenoyloxy) propane and 1-(*z,z,z,z,z,z*-docosa-4,7,10,13,16,19-hexaenoyloxy)-2(S)-(*z,z,z*-octadeca-6,9,12-trienoyloxy)propane as a colourless oil.

Example 11

(±)-1-(1,2-dithiolane-3-pentanoyloxy)-2-(*z,z,z*-octadeca-6,9,12-trienoyloxy)propane and (±)-1-(*z,z,z*-octadeca-6,9,12-trienoyloxy)-2-(1,2-dithiolane-3-pentanoyloxy) propane

(Racemic diester of GLA and lipoic acid with 1,2-propane diol - mixture of positional isomers)

A mixture of 1,3-dicyclohexylcarbodiimide (720mg) and 4-(N,N-dimethylamino) pyridine (480mg) in *tert*-butyl methyl ether (15mL) was added to a mixture of lipoic acid (645mg) and (±)-1-(*z,z,z*-octadeca-6,9,12-trienoyloxy)propan-2-ol and (±)-2-(*z,z,z*-octadeca-6,9,12-trienoyloxy)propan-1-ol [prepared as in Example 7, Part 1] (1g) in *tert*-butyl methyl ether (30mL). The resulting mixture was stirred at room temperature under nitrogen for 5h, at which point tlc analysis indicated essentially complete reaction. The reaction mixture was diluted with hexane (50mL), filtered, concentrated and purified by silica gel chromatography to yield (±)-1-(1,2-dithiolane-3-pentanoyloxy)-2-(*z,z,z*-octadeca-6,9,12-trienoyloxy)propane and (±)-1-(*z,z,z*-octadeca-6,9,12-trienoyloxy)-2-(1,2-dithiolane-3-pentanoyloxy) propane as a viscous yellow oil.

Example 12

(±)-1-(*z,z,z*-octadeca-6,9,12-trienoyloxy)-2-(nicotinyloxy)propane and (±)-1-(nicotinyloxy)-2-(*z,z,z*-octadeca-6,9,12-trienoyloxy)propane
(Racemic diester of GLA and niacin with 1,2-propane diol - mixture of positional isomers)

A solution of 1,3-dicyclohexylcarbodiimide (2.11g) and 4-(N,N-dimethylamino) pyridine (1.41g) in dichloromethane (20mL) was added to a solution of niacin (1.31g) and (±)-1-(*z,z,z*-octadeca-6,9,12-trienoyloxy)propan-2-ol and (±)-2-(*z,z,z*-octadeca-6,9,12-trienoyloxy)propan-1-ol [prepared as in Example 7, Part 1] (3g) in methylene chloride (20mL). The reaction mixture was stirred at room temperature, reaction progress being monitored by tlc analysis. On completion, the reaction mixture was diluted with hexane, filtered, concentrated and purified by silica gel chromatography to yield (±)-1-(*z,z,z*-octadeca-6,9,12-trienoyloxy)-2-(nicotinyloxy)propane and (±)-1-(nicotinyloxy)-2-(*z,z,z*-octadeca-6,9,12-trienoyloxy)propane as a pale yellow oil.

Example 13

1-(1-(4-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetyloxy)-2(S)-(*z,z,z*-octadeca-6,9,12-trienoyloxy)propane and 1-(*z,z,z*-octadeca-6,9,12-trienoyloxy)-2(S)-(1-(4-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetyloxy)propane
(Enantiopure diester of GLA and indomethacin with 1,2-propane diol - mixture of positional isomers)

A solution of 1,3-dicyclohexylcarbodiimide (580mg) and 4-(N,N-dimethylamino) pyridine (380mg) in dichloromethane (10mL) was added to a solution of 1-(*z,z,z*-octadeca-6,9,12-trienoyloxy)propan-2(S)-ol and 2(S)-(*z,z,z*- octadeca-6,9,12-trienoyloxy)propan-1-ol [prepared as in Example 9, Part 2] (800mg) and indomethacin (930mg) in dichloromethane

(10mL). The resulting mixture was stirred at room temperature under nitrogen, reaction progress being monitored by tlc analysis. On completion, the reaction mixture was diluted with hexane, filtered, concentrated and purified by silica gel chromatography to yield 1-(1-(4-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetyloxy)-2(S)-(*z,z,z*-octadeca-6,9,12-trienoyloxy)propane and 1-(*z,z,z*-octadeca-6,9,12-trienoyloxy)-2(S)-(1-(4-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetyloxy)propane as a viscous yellow oil.

Example 14

1-(1-(*z,z,z*-octadeca-6,9,12-trienoyloxy)-2(S)-propyl)-4-(2-(2-methyl-5-nitroimidazoyl)ethyl)butane-1,4-dioate and 1-(2(S)-(*z,z,z*-octadeca-6,9,12-trienoyloxy)-1-propyl)-4-(2-(2-methyl-5-nitroimidazoyl)ethyl)butane-1,4-dioate
(Enantiopure diester of GLA and metronidazole succinate with 1,2-propane diol - mixture of positional isomers)

Part 1 - succinate monoester of 1-(*z,z,z*-octadeca-6,9,12-trienoyloxy)propan-2(S)-ol and 2(S)-(*z,z,z*-octadeca-6,9,12-trienoyloxy)propan-1-ol

A mixture of 1-(*z,z,z*-octadeca-6,9,12-trienoyloxy)propan-2(S)-ol and 2(S)-(*z,z,z*-octadeca-6,9,12-trienoyloxy)propan-1-ol [prepared as in Example 9, Part 2] (10g) and succinic anhydride (3g) in dry THF (100mL) was stirred at room temperature under nitrogen until a clear solution resulted. This solution was cooled to 0°C and a solution of 1,8-diazabicyclo[5.4.0]undec-7-ene (4.5mL) in dry THF (50mL) was added dropwise to it. After 3h, tlc analysis indicated that the reaction was essentially complete. The reaction mixture was diluted with diethyl ether (250mL) and washed with 2M hydrochloric acid (2x250mL), water (250mL) and brine (250mL), dried (sodium sulfate) and concentrated to dryness. This yielded the succinate monoester of 1-(*z,z,z*-octadeca-6,9,12-trienoyloxy)propan-2(S)-ol and 2(S)-(*z,z,z*-octadeca-6,9,12-trienoyloxy)propan-1-ol which was used without any further purification.

Part 2 - 1-(1-(*z,z,z*-octadeca-6,9,12-trienoyloxy)-2(S)-propyl)-4-(2-(2-methyl-5-nitroimidazoyl)ethyl)butane-1,4-dioate and 1-(2(S)-(*z,z,z*-octadeca-6,9,12-trienoyloxy)-1-propyl)-4-(2-(2-methyl-5-nitroimidazoyl)ethyl)butane-1,4-dioate

A solution of 1,3-dicyclohexylcarbodiimide (1.09g) and 4-(N,N-dimethylamino) pyridine in dichloromethane (10mL) was added to a mixture of succinate monoester of 1-(*z,z,z*-octadeca-6,9,12-trienoyloxy)propan-2(S)-ol and 2(S)-(*z,z,z*-octadeca-6,9,12-trienoyloxy)propan-1-ol (2g) and metronidazole (790mg) and the resulting mixture was stirred at room temperature under nitrogen, reaction progress being monitored by tlc analysis. On completion, the reaction mixture was diluted with hexane, filtered, concentrated and purified by silica gel chromatography to yield 1-(1-(*z,z,z*-octadeca-6,9,12-trienoyloxy)-2(S)-propyl)-4-(2-(2-methyl-5-nitroimidazoyl)ethyl)butane-1,4-dioate and 1-(2(S)-(*z,z,z*-octadeca-6,9,12-trienoyloxy)-1-propyl)-4-(2-(2-methyl-5-nitroimidazoyl)ethyl)butane-1,4-dioate as a pale yellow oil.

Example 15

1-(1-(*z,z,z*-octadeca-6,9,12-trienoyloxy)-2-propyloxycarbonyl)-*trans*-2-phenylcyclopropyl propanamide and 1-(2-(*z,z,z*-octadeca-6,9,12-trienoyloxy)-1-propyloxycarbonyl)-*trans*-2-phenylcyclopropyl propanamide
(Racemic diester of GLA and tranylcypromine succinate with 1,2-propane diol - mixture of positional isomers)

A solution of 1,3-dicyclohexylcarbodiimide (1.09g) and 4-(N,N-dimethylamino) pyridine in dichloromethane (10mL) was added to a mixture of succinate monoester of 1-(*z,z,z*-octadeca-6,9,12-trienoyloxy)propan-2-ol and 2-(*z,z,z*-octadeca-6,9,12-trienoyloxy)propan-1-ol (2g) and tranylcypromine (790mg) and the resulting mixture was stirred at room temperature under nitrogen, reaction progress being monitored by tlc analysis. On completion, the reaction mixture was diluted with hexane, filtered, concentrated and purified by silica gel chromatography to yield *trans*-1-(1-(*z,z,z*-octadeca-6,9,12-trienoyloxy)-2-propyloxycarbonylpropanoylamino)-2-phenylcyclopropane and *trans*-1-(2-(*z,z,z*-octadeca-6,9,12-trienoyloxy)-1-propyloxy carbonylpropanoylamino)-2-phenylcyclopropane as a pale yellow oil.

Example 16

1-(*z,z,z*-octadeca-6,9,12-trienoyloxy)-2(S)-(2(S)-amino-3-phenylpropionyloxy)propane and 1-(2(S)-amino-3-phenylpropionyloxy)-2(S)-(*z,z,z*-octadeca-6,9,12-trienoyloxy)propane.
(Enantiopure diester of GLA and phenylalanine with 1,2-propane diol - mixture of positional isomers)

Part 1 - 1-(*z,z,z*-octadeca-6,9,12-trienoyloxy)-2(S)-(2(S)-N-^{t}BOC-amino-3-phenylpropionyloxy)propane and 1-(2(S)-N-^{t}BOC-amino-3-phenylpropionyloxy)-2(S)-(*z,z,z*-octadeca-6,9,12-trienoyloxy)propane.

A solution of 1,3-dicyclohexylcarbodiimide (1.77g) and 4-(N,N-dimethylamino) pyridine (1.24g) in dichloromethane (30mL) was added with stirring to a solution of 1-(*z,z,z*-octadeca-6,9,12-trienoyloxy)propan-2(S)-ol and 2(S)-(*z,z,z*-octadeca-6,9,12-trienoyloxy)propan-1-ol [prepared as in Example 9, Part 2] (2.62g) and N-^{t}BOC phenylalanine (2.17g) in dichloromethane (30mL) at room temperature under nitrogen. Stirring was continued for 7h and the mixture stored overnight at 0°C. The mixture was purified by silica gel chromatography to yield the amino protected product as a yellow oil.

Part 2 - 1-(*z,z,z*-octadeca-6,9,12-trienoyloxy)-2(S)-(2(S)-amino-3-phenylpropionyloxy)propane and 1-(2(S)-amino-3-phenylpropionyloxy)-2(S)-(*z,z,z*- octadeca-6,9,12-trienoyloxy)propane

The amino protected product was dissolved in 10% anisole / trifluoroacetic acid (17mL) and left at room temperature under nitrogen for 30 minutes. After tlc analysis indicated that deprotection was complete, the mixture was purified by silica gel chromatography to yield 1-(*z,z,z*-octadeca-6,9,12-trienoyloxy)-2(S)-(2(S)-amino-3-phenylpropionyloxy)propane and 1-(2(S)-amino-3-phenylpropionyloxy)-2(S)-(*z,z,z*-octadeca-6,9,12-trienoyloxy)propane as a viscous yellow oil.

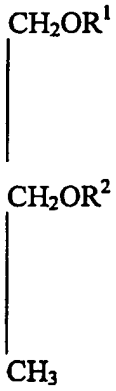
Example 17

(1-(z,z,z-octadeca-6,9,12 trienoxyloxy)-2-propyl)-(z,z,z-octadeca-6,9,12-trienyl) phosphate and (2-z,z-z-octadeca-6,9-12 trienoyloxy)-1-propyl)-(z,z,z-octadeca-6,9-12-trienyl)phosphate. *Racemic phosphodiester of GLA and (1-and-2-monoesters of GLA with 1,2-propane diol)*

Triethylamine (7.5mL) was added to a solution of freshly distilled phosphorus oxychloride (1.26g) in anhydrous THF (7.5ml) at 0°C. After 15 min. a solution of 1-(z,z,z-octadeca-6,9,12-trienoyloxy)-2-propanol and 2-(z,z,z-octadeca-6,9,12-trienoyloxy)-1-propanol (2.5g) in anhydrous THF (7.5mL) was added dropwiseover a period of 30 min. at 0°C. Stirring at this temperature was continued for 30 min. after the end of addition. Then, z,z,z-octadeca-6,9,12 trienol (1.98g) in anhydrous THF (5mL) was added dropwise at 10°C and the resultant mixture was stirred at 10°C for 1 h and then overnight, warming up to room temperature. Triethylamine (8mL) and water (20mL) were added. The mixture was stirred under nitrogen in an ice bath for 1h. acidified to pH1 with 2M hydrochloric acid and extracted into ethyl acetate (80mL) and methanol (20mL). The extract was dried, concentrated and purified by silica gel chromatography to yield (1-(z,z,z-octadeca-6,9,12-trienoyloxy)-2-propyl)-(z,z,z-octadeca 6,9,12-trienyl)phosphate and (2-(z-z-z-octadeca 6-9-12-trienoxyloxy)-1-propyl)-(z-z-z-octadeca-6,9-12 trienyl)phosphate.

CLAIMS

1. Compounds of the following 1,2-propane diol linked structure, when for use in therapy:-



wherein R^1 or R^2 comprise an acyl or fatty alcohol group derived from a C_{12-30} preferably C_{16-30} fatty acid desirably with two or more cis or trans double bonds, or any other nutrient, drug or other bioactive residue, but such that at least one of R^1 or R^2 comprises an acyl or fatty alcohol group as defined above, and wherein where both R^1 or R^2 comprise acyl or fatty alcohol groups they may be the same or different.

2. A compound according to claim 1 wherein the R^1 and/or R^2 group comprises a phosphate, succinate or other difunctional acid group adjacent to the 1,2-propane diol residue, particularly when R^1 or R^2 or each of them is a nutrient, drug or other bioactive having a hydroxy or amino function.

3. A compound according to claim 1 or 2, wherein the fatty acid is an n-6 or n-3 series essential fatty acid or oleic acid or columbinic acid or parinaric acid or conjugated linoleic acid.

4. A compound according to claim 3 wherein the fatty acid is gamma-linolenic acid, dihomo-gamma-linolenic acid, arachidonic acid, adrenic acid, stearidonic acid, eicosapentaenoic acid, docosapentaenoic acid n-3, docosahexaenoic acid or conjugated linoleic acid.

5. A compound according to claim 1, 2, 3 or 4 where R^1 or R^2 comprises a drug or other active required to cross lipid membranes in the body to exert its action whether in entry to or movement within a cell in which it is to act, or in passing the skin, blood-brain or other barrier.

6. A compound according to claim 1, 2, 3 or 4, wherein irrespective of any crossing of lipid membranes one at R^1 or R^2 is a drug, vitamin, amino acid, anti-oxidant or other active which is required to have an action additive to, complementary to, or synergistic with the other of R^1 and R^2.

7. A method of improving the transport of a drug or other active across lipid membranes in the body, or of securing an action as set out in claim 6, characterised by administration of the active in the form of a compound as in any preceding claim.

8. A method of manufacture of a medicament for therapy involving transport of a drug or other active across lipid membranes in the body, or involving securing an action as set out in claim 6, characterised by the use in, or as, the medicament of a compound as in any preceding claim 1 to 6.

9. A compound or any group of compounds specifically as set out herein, being within claim 1, 2, 3, or 4, per se or for use in therapy generally or specifically.

10. Per se, or for use in therapy generally or specifically, any compound or group of compounds as set out herein, being novel as such or in such use.

11. Pharmaceutical use of a compound as set out in any one of claims 1 to 6.

12. Use in the preparation of formulations for care of the skin or treatment of skin disorders of a compound as set out in any one of claims 1 to 6.

13. Use in the preparation of a food, food additive or food supplement of a compound as set out in any one of claims 1 to 6

14. A method of treating a disease by using a compound as set out in any one of claims 1 to 6.

15. A method of preparing a medicament for oral, parenteral, enteral, topical or other use by employing a compound as set out in any one of claims 1 to 6.

16. 1,2-propane diol as derivatives containing: two fatty acids in which one fatty acid is GLA or DGLA and the other is GLA, DGLA, SA, EPA, DHA, cLA (conjugated linoleic acid) or CA (columbinic acid) for the treatment of. -

(a) complications of diabetes, particularly neuropathy and retinopathy; and improvement of responses to insulin in diabetes and pre-diabetes;

(b) cancers;

(c) osteoarthritis;

(d) rheumatoid arthritis;

(e) other inflammatory and auto-immune diseases including Sjogren's syndrome, systemic lupus, ulcerative colitis, Crohn's disease and uveitis;

(f) respiratory diseases including asthma;

(g) neurological disorders including multiple sclerosis, Parkinson's disease and Huntington's chorea;

(h) renal and urinary tract disorders;

(i) cardiovascular disorders;

(j) degenerative diseases of the eye including retinitis pigmentosa and senile macular degeneration;

(k) psychiatric disorders including schizophrenia, Alzheimer's disease, attention deficit disorder, alcoholism and depression

(l) prostatic hypertrophy and prostatitis;

(m) impotence and male infertility;

(n) mastalgia;

(o) male pattern baldness;

(p) osteoporosis;

(q) dermatological disorders, including atopic eczema, hand eczema, psoriasis, urticaria and allergic disorders;

(r) dyslexia and other learning disabilities;

(s) cancer cachexia.

17. 1,2-propane diol as derivatives containing two fatty acids in which one fatty acid is AA and the other is AA, GLA, DHA, DGLA or EPA for treatment of the disorders set out in claim 16 and especially (a), (g), (i), j), (k), (q) and (r),

18. 1,2-propane diol as derivatives containing two fatty acids in which one fatty acid is EPA and the other is EPA or DHA for the treatment of any of the disorders set out in claim 16 but especially (b), (c), (d), (e), (f), (g), (h), (i), j), (k), (p), (r) and (s).

19. 1,2-propane diol as set out in claims 16 to 18 in which the diol is used as a component of a food, particularly of a functional food or nutraceutical for the promotion of health, as a nutritional supplement or as a food additive.

20. 1,2-propane diol as set out in claims 16 to 18 in which the diol is used for enteral or parenteral administration in products used in clinical nutrition.

21. 1,2-propane diol as set out in claims 16 to 18 in which the diol is used as a component of a cosmetic or other preparation used in the care of the skin or the hair.

22. Per se, 1,2-propane diol as set out in claims 16 to 18.

23. 1,2-propane diol as derivatives in which one position is occupied by a fatty acid drawn from GLA, DGLA, AA, SA, cLA, EPA or DHA and the other position is occupied by an

agent, selected from the following list, whose chemical structure is such that it can be linked to the 1,2-propane diol by one of the linkages described herein:

(a) tryptophan for the treatment of any disease but particularly for psychiatric, neurological, behavioural, pain and other disorders and especially depression, sleep and migraine;

(b) phenylalanine for the treatment of any disease, but especially depression, multiple sclerosis and chronic fatigue syndrome;

(c) arginine for the treatment of any disease but particularly diseases in which the production of nitric oxide is defective;

(d) caoritine or caoritine derivatives for the treatment of any disease but especially muscle weakness. cardiac failure, chronic fatigue syndrome, Alzheimer's disease, and peripheral neuropathies;

(e) any other amino acid or related substance for the treatment of any disease or aminolevulinic acid or derivative thereof for the treatment of any disease but especially cancers;

(f) adenylosuccinate or related substances for the treatment of any disease but especially muscular dystrophy, cardiac failure, chronic fatigue and Alzheimer's disease and other dementias;

(g) aspirin, salicylic acid, indomethacin, ibuprofen, or any other non steroidal antiinflammatory drug for the treatment of any disease but especially of inflammatory disorders, of pain, of Alzheimer's disease and other dementias and of any disease in which platelet aggregation should be inhibited;

(h) any antibiotic for the treatment of any appropriate infectious disease but especially tetracycline, clindamycin, minocycline, chlortetracycline and erythromycin for the treatment of acne;

(i) any anti-malarial or anti-protozoal drug for the treatment of any disease, but especially chloroquine, mepacrine, quinacrine and mefloquine for the treatment of malaria, protozoal disorders, inflammatory disorders and schizophrenia;

(j) any antifungal drug for the treatment of any disease but especially metronidazole and antifungal imidazoles and nitroimidazoles and amphotericin for the treatment of fungal infections of various types;

(k) any anti-inflammatory steroid for the treatment of any disease but especially hydrocortisone and betamethasone for the treatment of skin disorders and beclomethasone and budesonide for the treatment of asthma;

(l) any gonadal steroid for the treatment of any disease but especially oestrogens and progestogens for the treatment of ovarian deficiency and osteoporosis and androgens for the treatment of testicular deficiency;

(m) any adrenal steroid for the treatment of any disease, but especially dehydroepiandrosterone for the treatment of disorders associated with ageing;

(n) any retinoid for the treatment of any disease but especially tretinoin and isotretinoin for the treatment of dermatological disorders and for use in skin care;

(o) any anticancer agent for the treatment of cancer;

(p) any antipsychotic agent for the treatment of schizophrenia and other psychoses;

(q) any antidepressive agent for the treatment of any disease but especially for the treatment of depression;

(r) any anti-anxiety agent for the treatment of any disease, but especially for the treatment of anxiety and panic attacks;

(s) any immunosuppressive agent for the treatment of any disease but especially cyclosporine and tacrolimus for the control of immunity after organ transplantation and for the treatment of autoimmune and inflammatory disorders

including psoriasis, eczema, asthma, rheumatoid arthritis and inflammatory bowel disease;

(t) any proton pump inhibitor or H2 antagonist for the treatment of any disease but especially diseases associated with excess gastric acid production or reduced defences against gastric acidity;

(u) any diuretic for any disease, but especially for diseases associated with fluid retention and hypertension;

(v) any calcium antagonist used for any disease but especially for cardiovascular diseases;

(w) any angiotensin converting-enzyme inhibitor or angiotensin antagonist used for any disease but especially for cardiovascular diseases;

(x) any beta-blocker used for any disease but especially for cardiovascular disorders;

(y) any antiepileptic drug used for any disease, but especially phenytoin, carbamazepine, valproate, ethosuximide, vigabatrin or lamotrigine for the treatment of epilepsy;

(z) any hypolipidaemic agent for the treatment of any disease but especially fibrates and statins used for cholesterol lowering and cholesterol modification;

(aa) any oral hypoglycaemic or insulin-sensitising agents used in the management of diabetes;

(bb) any bisphosphonates used in the management of osteoporosis, Paget's disease or cancer;

(cc) any contrast agents used in radiology including diatrizoate compounds, iodipamide, ioglycamates, iopanoates, iophendylate, iothalamate, ioxaglate, metrizamide and related compounds;

(dd) any peptide or protein for use in the treatment of diseases for which the peptide or protein itself is used, including insulin, calcitonin, erythropoietin and other peptides ;

(ee) any vitamin used in the treatment of any disease, or used in foods, nutritional supplements or food additives as a way of providing the vitamin effectively;

(ff) any antioxidant used in the management of any disease, but especially for those diseases in which antioxidants may be especially beneficial including cardiovascular diseases, cancer and inflammatory disorders and any antioxidant used as a food or other preservative or as a component of a food, food additive or nutritional supplement,

(gg) any porphyrin chlorin or bacteriochlorin-based drug especially tetrakis (hydroxy phenyl) derivatives thereof used in photodynamic therapy of cancers.

24. Per se, 1,2-propane diol as set out in claim 23.

INTERNATIONAL SEARCH REPORT

Intern ...nal Application No
PCT/GB 97/02932

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07C69/587 A61K31/23 C07D339/04 C07D213/68 C07D233/94
A61K31/44 C07C43/15

According to International Patent Classification(IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07C A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EMIL ALBERHALDEN ET AL.: "Versuche über die Darstellung optisch-aktiver Fette.I.Synthese optisch-aktiver Halogenhydrine. " BERICHTE DER DEUTSCHEN CHEMISCHEN GESELLSCHAFT., 1914, WEINHEIM DE, pages 1856-1866, XP002053371 see page 1861, paragraph 5 - page 1862, paragraph 4 ---	1,3
X	EP 0 407 959 A (LION CORPORATION) 16 January 1991 see page 11; examples 31,32 ---	1,3
A	EP 0 611 569 A (SCOTIA HOLDINGS PLC) 24 August 1994 see the whole document ---	1
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

1

Date of the actual completion of the international search	Date of mailing of the international search report
27 January 1998	12/03/1998

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Kinzinger, J

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INTERNATIONAL SEARCH REPORT

Inter. .onal Application No
PCT/GB 97/02932

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
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